OVARIAN CANCER

New studies add to our understanding of which women may benefit from screening. The goal of improving overall survival among women who have this malignancy is elusive, however.

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IN THIS ARTICLE

To improve outcomes in women who have ovarian cancer—the deadliest gynecologic malignancy in the United States—we need to pursue a number of investigative approaches:

- We need to determine how to diagnose the disease in its early stages. At present, fewer than 20% of ovarian cancer cases are identified while disease is localized to the adnexae. Although a symptom index has been suggested as a useful tool to highlight women at risk for ovarian cancer, its appropriate implementation and effectiveness have yet to be determined.[1] Moreover, the symptoms of ovarian cancer are vague and may not become apparent until after the disease has metastasized. Might screening trials detect ovarian cancer in its earlier stages? Are there harms involved in screening women with transvaginal ultrasonography (TVUS) and cancer antigen (CA) 125?
- We need new first-line agents to treat ovarian cancer. Traditional therapy is surgical cytoreduction followed by platinum-based chemotherapy. More recently, the addition of intraperitoneal chemotherapy has prolonged survival by approximately 16 months in women who have advanced disease.[2] Despite this advance, the relapse rate remains high. What new therapies can we offer in addition to traditional platinum-based chemotherapy?
- Ovarian cancer recurs in most women, and the response to subsequent therapy is short-lived.[3,4] Novel biologic agents may offer new hope as a means of treating recurrent disease with greater specificity and lower toxicity. Do any biologic agents increase survival and reduce the toxicity of treatment?

In this article, we highlight notable studies published in the past year that address these questions.

Screening for ovarian cancer is not useful in average-risk women

Buys SS, Partridge E, Black A, et al; PLCO Project Team. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Randomized Screening Trial. JAMA. 2011;305(22):2295–2303.

Gilbert L, Basso O, Sampalis J, et al; DOvE Study Group. Assessment of symptomatic women for early diagnosis of ovarian cancer: results from the prospective DOvE pilot project. Lancet Oncol. 2012;13(3):285–291.

The Prostate, Lung, Colorectal and Ovarian (PLCO) trial addresses the utility of screening for ovarian cancer using two readily available tests—TVUS and CA 125.

Effective screening for any disease requires the following:

- The disease must have a presymptomatic stage during which diagnosis leads to better outcomes (compared with waiting until the onset of symptoms)
- The screening test must be acceptable to the population in which it is used
- The test must lead to a reduction in morbidity and mortality that outweighs the harms of false-positive tests
- The benefits of the test must be achieved at an acceptable level of risk.[5]

The PLCO trial was designed to determine the effect of specific ovarian cancer screening tests on cause-specific mortality. Women aged 55 to 74 years were randomly assigned to annual screening with TVUS and CA 125 or to standard gynecologic care. A CA-125 level of 35 or higher was classified as abnormal, as were TVUS findings of enlarged ovaries or solid or papillary components. The trial had 88% power to detect a 35% reduction in ovarian cancer mortality using a one-side α of 0.05.

Early results demonstrated that a large number of surgeries would be required to detect one case of ovarian cancer. Mortality data from the study only recently matured.[6]

Details of the PLCO trial

Approximately 39,000 women were allocated to each arm of the PLCO trial and followed for 6 years. Ovarian cancer was diagnosed in 212 and 176 women in the screening and usual-care groups, respectively (relative risk, 1.21; 95% confidence interval [CI], 0.99–1.48). Equal percentages of women in each group were given a diagnosis of Stage III/IV cancer.

No survival benefit was seen in the screening group. Overall, 3,285 women had a false-positive screening test, with 33% undergoing surgery (21% surgical complication rate).

Barriers to effective screening

One of the major obstacles to the development

WHAT THIS EVIDENCE MEANS FOR PRACTICE

TVUS and CA 125 increase the number of cases of ovarian cancer that are diagnosed but do not provide a survival benefit. Identification of cases in the PLCO trial was, therefore, likely the result of lead-time bias—cases of ovarian cancer were detected sooner but not at an early stage.

Routine screening with TVUS and CA 125 are not recommended at this time for women at average risk for ovarian cancer. These and similar screening methods lead to a significant false-positive rate, with surgeries performed for benign indications and a high risk of surgical complications. Further studies to improve the sensitivity and specificity of these tests in women at average risk for ovarian cancer are ongoing.[7]

Women who have an elevated risk of ovarian cancer, such as women who carry the BRCA mutation or who have a family history of ovarian cancer, may benefit from routine screening because of increased disease prevalence in this population, although studies are needed to determine the best utilization of screening tests.

Women who have symptoms of ovarian cancer should undergo thorough evaluation that may lead to earlier diagnosis and improved outcomes.

Effect of disease prevalence on population-based screening

Specificity of the screening test (%)	Positive predictive value (%)			
	50% prevalence	10% prevalence	1% prevalence	Ovarian cancer (1 case in every 2,500 women)
90	91	53	9	0.4
95	95	69	17	0.8
99	99	92	50	4
99.9	99.9	99	91	29

of an accurate screening test for ovarian cancer has been the low prevalence of the disease. The relationship between sensitivity, specificity, prevalence, and positive predictive value (PPV) is demonstrated in the **TABLE**. With sensitivity of 100% and specificity of 95%, the PPV for ovarian cancer screening with TVUS and CA 125 is only 1%. Ovarian cancer has an annual prevalence of approximately 1 case in every 2,500 women.

FAST TRACK

TVUS and CA-125 testing in patients with ovarian cancer symptoms may help identify the disease in its early stage

Details of the trial by Gilbert and colleagues

In a recent pilot study, Gilbert and colleagues prospectively analyzed the utility of disseminating information about the symptoms of ovarian cancer to the general public. Following dissemination of information, women who were 50 years or older and who had experienced at least one ovarian cancer symptom longer than 2 weeks underwent CA-125 testing and TVUS. If both tests were normal, CA 125 was repeated; if it was normal again, the patient was discharged from the study.

Patients who had abnormal findings on either test repeated both screening tests, with additional testing performed as necessary. Outcomes of these women were compared with those of women who had been referred to the gynecologic oncology clinic.

Among 1,455 eligible patients, 11 cases of invasive ovarian cancer were diagnosed, four of which (36%) represented early-stage disease. Median CA-125 levels were lower in the study group. In addition, more women in the study group had early-stage disease that was completely resectable, compared with the clinic group, although this difference did not reach statistical significance.

Most cases of ovarian cancer in this study originated in the fallopian tube or peritoneum—not the ovary. In addition to the cases of ovarian cancer, 11 cases of uterine cancer were diagnosed. No patients underwent unwarranted major surgery, and none who were discharged from the study had a diagnosis of gynecologic cancer by 7 months of follow-up.

Did you read these articles on OVARIAN CANCER?

›› **Risk of 3 types of ovarian cancer higher in women who have endometriosis** (March 2012)

›› **Ovarian stimulation ups risk of ovarian tumors in later life** (October 2011)

›› **Can a novel risk-scoring system for ovarian cancer predict who is most likely to develop disease?** (July 2011)

They're available in the archive at obgmanagement.com

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Adding bevacizumab to standard chemotherapy prolongs the progression-free interval but not overall survival

Burger RA, Brady MF, Bookman MA, et al; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473–2483.

Perren TJ, Swart AM, Pfisterer J, et al; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365(26):2484–2496.

FAST TRACK

Bevacizumab increased progression-free survival from 1.7 to 3.8 months

Epithelial ovarian cancer frequently expresses vascular endothelial growth factor (VEGF). Lower levels of VEGF are associated with decreased formation of new blood vessels and increased survival.

Bevacizumab is a monoclonal antibody that binds to VEGF and inhibits its biological activity. It has proved to be effective in the treatment of colorectal, lung, and brain cancers.

These two recent trials evaluated the benefit of adding bevacizumab to first-line chemotherapy for ovarian cancer. In the Gynecologic Oncology Group (GOG) trial (Protocol #218), investigators evaluated women with Stage III/IV ovarian cancer. The ICON7 trial also included women who had high-risk early-stage disease.

Both trials randomly assigned women to first-line chemotherapy with carboplatin and paclitaxel plus either bevacizumab or placebo. After completion of initial treatment, maintenance therapy continued for an additional 12 to 16 cycles.

In a third arm of GOG 218, bevacizumab was administered only during the six cycles of initial chemotherapy without any maintenance treatment.

Both trials were powered to detect an improvement in progression-free survival, not overall survival.

Findings of the trials

In GOG 218, approximately 600 women were allocated to each of its three arms. In ICON7, approximately 750 women were allocated to each of its two arms.

Both trials demonstrated a benefit when bevacizumab was added to initial treatment, followed by maintenance therapy. The hazard ratio for recurrent disease was 0.72 (95% CI, 0.63–0.82) and 0.81 (95% CI, 0.70–0.94) in the two trials, respectively, with increased progression-free survival of 1.7 to 3.8 months.

Neither study demonstrated a significant increase in overall survival. Women who did not receive bevacizumab maintenance therapy experienced no benefit from treatment.

No significant differences were observed between treatment groups. Bevacizumab was generally well tolerated. The gastrointestinal perforation rate with bevacizumab therapy ranged from 1% to 3%.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

When it is administered with initial chemotherapy and continued as maintenance therapy, bevacizumab leads to overall improvement in progression-free survival without a significant increase in overall survival.

We need additional studies to identify molecular markers that will predict the response to bevacizumab and other biologic treatments and determine whether any subgroup of patients will experience greater benefit from the addition of bevacizumab to standard chemotherapy regimens. The findings of such trials will allow us to better tailor treatment to each ovarian cancer patient.

Olaparib significantly increases progression-free survival in women who have platinum-sensitive, recurrent ovarian cancer

Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382–1392.

Approximately 15% of epithelial ovarian cancers demonstrate a mutation in one of the BRCA genes, which function as an important component of DNA repair. Another 35% acquire a similar phenotype due to somatic mutations or silencing of the BRCA genes.

The poly ADP ribose polymerase (PARP) protein plays a role in the repair of single-strand breaks. Tumors with the mutated BRCA phenotype are particularly sensitive to PARP inhibitors[8] because PARP inhibition leads to double-strand DNA breaks that cannot be repaired in BRCA mutated tumors.[9]

A recent phase II trial in recurrent ovarian cancer demonstrated a nearly twofold response rate to olaparib, a PARP inhibitor, among women who had a known BRCA mutation.[10]

Details of the trial

This study by Ledermann and colleagues was designed to determine the effect of olaparib in all women who have ovarian cancer. It was designed as a randomized, double-blind, phase II trial. Women who had recurrent ovarian, fallopian-tube, or primary peritoneal cancer who were sensitive to platinum and had an objective response to their most recent chemotherapy were randomly assigned to oral olaparib (twice daily dosing) or placebo until such time as disease progressed. The trial had 80% power to detect a 25% decrease in the risk of progression in the olaparib group, with an α less than 0.20.

Two hundred sixty-five women were allocated to each of the two treatment arms. Women treated with olaparib had a risk of recurrence or death that was 35% (95% CI, 25%–49%) the risk among women treated with placebo; they also had a median progression-free survival that was 4 months longer. This response was seen in women with and without BRCA mutations.

Overall, olaparib was well tolerated, although women randomized to the olaparib group had a higher rate of moderate to severe side effects, mostly due to a higher rate of nausea, vomiting, fatigue, and anemia.

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FAST TRACK

Progression-free survival for women receiving olaparib was a median 4 months longer than for women on placebo

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Maintenance therapy with oral olaparib significantly increases progression-free survival in women who have platinum-sensitive, recurrent ovarian cancer regardless of their BRCA-mutation status. No significant difference was seen in overall survival at an interim analysis.

Although olaparib is not FDA approved for treatment in patients, these results likely will renew interest in further studies to identify biomarkers to identify patients who are best suited for this treatment.

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